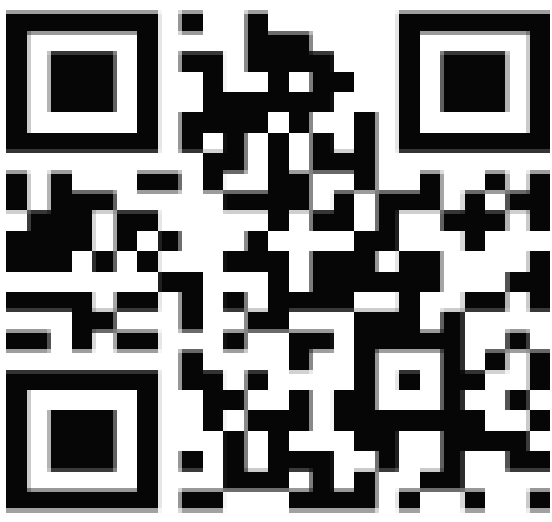


Challenging the pressure on NHS resources: could 48-hour continuous subcutaneous infusions (CSCIs) help? A systematically -structured review of the current evidence base.

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Background

The majority of patients express a preference to die at home, yet the most commonly recorded place of death is hospital; in 2012, 36.7% of deaths in Liverpool occurred in the person’s usual place of residence. With an ageing population, NHS resources will be placed under increasing pressure to meet the needs and care preferences of chronically ill patients<sup>1,2</sup>.

Innovative approaches to existing therapies are one way to improve care and maximise service delivery. For example, the ability to deliver prescribed medication by CSCI over 48 hours may have numerous benefits in both patient care and health service resource utilisation: current practice limits infusion time to a maximum of 24 hours due to available chemical and microbiological stability data.

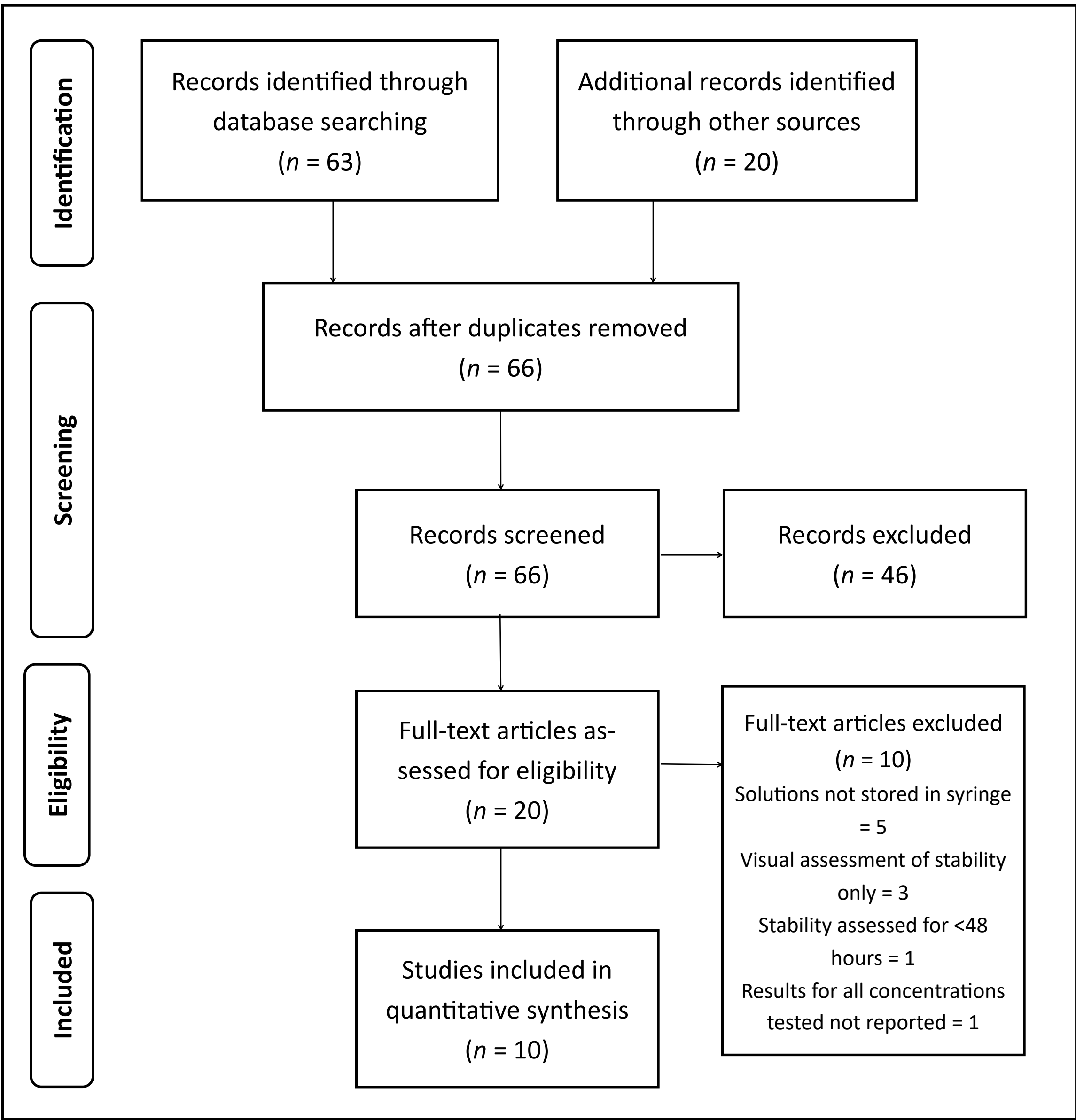
Aims

To examine and present the evidence on stability of 48 hour multiple-drug syringes/CSCIs in current clinical practice.

Methods

Three electronic databases (CINAHL, EMBASE and MEDLINE) and grey literature were systematically searched using PRISMA Guidance. Studies published in English reporting empirical data on the chemical or microbiological stability of continuous subcutaneous infusions or solutions stored in polypropylene syringes, were included.

Figure 1: PRISMA flowchart



Results

Chemical compatibility and stability of 51 different combinations of 12 drugs were reported across the ten studies included in this review (Table 1). Of the 51 combinations reported, all 51 were assessed as being chemically compatible after 48 hours at ambient temperatures (20-26°C). Nine of the thirteen drugs included are regularly utilised in the prescribing of CSCIs in the United Kingdom (midazolam, dexamethasone, hyoscine-N-butylbromide, haloperidol, fentanyl, diamorphine, cyclizine, metoclopramide and glycopyrrolate).

Results (cont.)

Midazolam appeared to be drug at greatest risk of clinically significant chemical degradation due to its pH dependent ring structure<sup>3</sup>. Microbiological stability was only reported for one combination.

Table 1: Summary of drug combinations and stability reported in reviewed articles

Study, Year and Country	Drug combination reported	Incompatibility observed?
Good et al; 2004; Australia	Midazolam hydrochloride 2.5mg + Dexamethasone sodium phosphate 4mg	No
	Midazolam hydrochloride 2.5mg + Dexamethasone sodium phosphate 2mg	No
	Midazolam hydrochloride 5mg + Dexamethasone sodium phosphate 2mg	No
	Midazolam hydrochloride 7.5mg + Dexamethasone sodium phosphate 2mg	Yes @ 37°C
Wilson et al; 1998; Australia	Fentanyl citrate 100mcg + Midazolam hydrochloride 5mg	No
	Fentanyl citrate 100mcg + Midazolam hydrochloride 7.5mg	No
	Fentanyl citrate 300mcg + Midazolam hydrochloride 5mg	No
	Fentanyl citrate 300mcg + Midazolam hydrochloride 7.5mg	Yes @ 37°C
	Fentanyl citrate 600mcg + Midazolam hydrochloride 15mg	No
	Fentanyl citrate 600mcg + Midazolam hydrochloride 5mg	Yes @ 37°C
Negro et al; 2006; Spain	Morphine hydrochloride 100mg + Haloperidol lactate 25mg + Hyoscine-N-butylbromide 300mg	No
	Morphine hydrochloride 100mg + Haloperidol lactate 37.5mg + Hyoscine-N-butylbromide 300mg	No
	Morphine hydrochloride 100mg + Haloperidol lactate 25mg + Hyoscine-N-butylbromide 400mg	No
	Morphine hydrochloride 100mg + Haloperidol lactate 37.5mg + Hyoscine-N-butylbromide 400mg	No
	Morphine hydrochloride 300mg + Haloperidol lactate 25mg + Hyoscine-N-butylbromide 300mg	No
	Morphine hydrochloride 300mg + Haloperidol lactate 37.5mg + Hyoscine-N-butylbromide 300mg	No
	Morphine hydrochloride 300mg + Haloperidol lactate 25mg + Hyoscine-N-butylbromide 400mg	No
	Morphine hydrochloride 300mg + Haloperidol lactate 37.5mg + Hyoscine-N-butylbromide 400mg	No
	Morphine hydrochloride 600mg + Haloperidol lactate 25mg + Hyoscine-N-butylbromide 300mg	No
	Morphine hydrochloride 600mg + Haloperidol lactate 37.5mg + Hyoscine-N-butylbromide 300mg	No
	Morphine hydrochloride 600mg + Haloperidol lactate 25mg + Hyoscine-N-butylbromide 400mg	No
	Morphine hydrochloride 600mg + Haloperidol lactate 37.5mg + Hyoscine-N-butylbromide 400mg	No
Peterson et al; 1998; Australia	Fentanyl citrate 1000mcg + Hyoscine-N-butylbromide 30mg + Midazolam hydrochloride 15mg	No
	Fentanyl citrate 1000mcg + Metoclopramide hydrochloride 20mg + Midazolam hydrochloride 15mg	No
Barcia et al; 2003; Spain	Haloperidol lactate 18.75mg + Hyoscine-N-butylbromide 150mg	No
	Haloperidol lactate 18.75mg + Hyoscine-N-butylbromide 300mg	No
	Haloperidol lactate 18.75mg + Hyoscine-N-butylbromide 600mg	No
	Haloperidol lactate 37.5mg + Hyoscine-N-butylbromide 150mg	No
	Haloperidol lactate 37.5mg + Hyoscine-N-butylbromide 300mg	No
	Haloperidol lactate 37.5mg + Hyoscine-N-butylbromide 600mg	No
	Haloperidol lactate 75mg + Hyoscine-N-butylbromide 150mg	Yes, @ 4°C and 25°C
	Haloperidol lactate 75mg + Hyoscine-N-butylbromide 300mg	Yes, @ 4°C and 25°C
Barcia et al; 2005; Spain	Morphine hydrochloride 100mg + Hyoscine-N-butylbromide 200mg	No
	Morphine hydrochloride 100mg + Hyoscine-N-butylbromide 300mg	No
	Morphine hydrochloride 100mg + Hyoscine-N-butylbromide 400mg	No
	Morphine hydrochloride 300mg + Hyoscine-N-butylbromide 200mg	No
	Morphine hydrochloride 300mg + Hyoscine-N-butylbromide 300mg	No
	Morphine hydrochloride 300mg + Hyoscine-N-butylbromide 400mg	No
	Morphine hydrochloride 600mg + Hyoscine-N-butylbromide 200mg	No
	Morphine hydrochloride 600mg + Hyoscine-N-butylbromide 300mg	No
	Morphine hydrochloride 600mg + Hyoscine-N-butylbromide 400mg	No
	Morphine hydrochloride 600mg + Hyoscine-N-butylbromide 400mg	No
Jäppinen et al; 1999; Finland	Buprenorphine hydrochloride 4mg + Haloperidol lactate 5mg + Glycopyrronium bromide 1.2mg	No
Targett et al; 1997; Australia	Morphine tartrate 400mg + Dexamethasone sodium phosphate 8mg + Droperidol 2mg + Hyoscine-N-butylbromide 20mg + Midazolam hydrochloride 8mg	Yes @ 22°C
	Morphine tartrate 40mg + Dexamethasone sodium phosphate 8mg + Droperidol 2mg + Hyoscine-N-butylbromide 20mg + Midazolam hydrochloride 5mg	No
Allwood; 1991; UK	Diamorphine hydrochloride 200mg + Haloperidol lactate 7.5mg	No
	Diamorphine hydrochloride 20mg + Cyclizine lactate 67mg	No
	Diamorphine hydrochloride 200mg + Cyclizine lactate 67mg	No
	Diamorphine hydrochloride 50mg + Haloperidol lactate 2.5mg	No
Collins et al; 1990; UK	Diamorphine hydrochloride 50mg + Haloperidol lactate 2.5mg	No
	Diamorphine hydrochloride 100mg + Haloperidol lactate 2.5mg	No

Conclusion

There is currently limited evidence for the physical, chemical and microbiological stability of solutions for continuous subcutaneous infusion over a period of 48 hours. More stability data is required before the use of 48-hour CSCIs can be evaluated for use within clinical practice. The range of temperatures at which stability is tested highlights the need for consensus on how stability/compatibility should be structured.

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